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Autoimmune enteropathy: a systematic review of reported cases, diagnostic patterns, treatment and outcomes (1997-2025)

Thomas Stirrat[a], Priyanka Solanky[b], Varat Ransibrahmanakul[b], Michael Flatley[c], Soham Apte[d], Lovedeep Singh[b], Olivia Allen[b], Priyanka Kanth[e]

David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; Georgetown University School of Medicine, Washington, DC, USA; Medical College of Wisconsin, Milwaukee, WI, USA; Kentucky College of Osteopathic Medicine, Pikeville, KY, USA; MedStar Georgetown University Hospital, Washington, DC, USA

Abstract

Background Autoimmune enteropathy (AIE) is a rare immune-mediated cause of non-celiac villous atrophy and malabsorptive diarrhea. We synthesized reported adult AIE cases to describe diagnostic patterns, treatments and outcomes.

Methods We systematically reviewed published adult AIE reports (1997-2025). Data were extracted with a standardized form and summarized descriptively using variable-specific denominators.

Results Fifty-five publications described 119 unique adult cases. Median age was 49 years (range 18-82), and 70 patients (58.8%) were female. Diarrhea was reported in 118/119 cases and present in all cases when reported. An initial alternative diagnosis was documented in 22 cases, most often celiac disease/refractory celiac disease (10/22) or inflammatory bowel disease (IBD)/colitis (4/22). Small-bowel involvement was universal when anatomic extent was reported (102/102), and colonic involvement was present in 37/52 cases with explicit reporting. Celiac serologies were often negative or unclear; anti-enterocyte antibody testing was frequently reported (107 cases), with 25 positive, 20 negative and 62 unclear results. Reported management was dominated by systemic corticosteroids (78/80 when exposure was documented), frequent steroid-sparing immunosuppression/biologics, and parenteral nutrition (28/28 when explicitly reported). Among cases with explicit outcome reporting, relapse occurred in 17/27 and death in 7/18; these selected proportions should not be interpreted as population rates.

Conclusions Adult AIE commonly mimics celiac disease/IBD and is best recognized through clinicopathologic patterning plus exclusion of mimickers. Standardized registries are needed to refine diagnosis and durable steroid-sparing treatment.

Keywords Autoimmune enteropathy, scoping review, case series, adult cohort, immunology

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Introduction

Autoimmune enteropathy (AIE) is a rare immune-mediated cause of non-celiac villous atrophy that presents with chronic watery diarrhea and malabsorption and does not improve with dietary elimination. First recognized in infancy in association with anti-epithelial autoantibodies [1], adult AIE was later described as a severe sprue-like syndrome with villous atrophy, negative celiac serologies, and poor response to a gluten-free diet, often alongside systemic autoimmunity [2,3]. Adult AIE remains exceptionally uncommon and likely under-recognized, because diagnostic criteria and access to specialized testing vary and there is substantial clinical overlap with other enteropathies [4].

Diagnosing adult AIE is challenging, because seronegative villous atrophy has a broad differential diagnosis, including refractory celiac disease, immunodeficiency-associated enteropathy, lymphoproliferative disorders, graft-versus-host disease-like injury patterns, and medication-associated enteropathy [3,5]. Clinically indistinguishable drug-related enteropathy, most notably with olmesartan, can resolve after medication withdrawal, underscoring the importance of careful

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Correspondence to: Thomas Stirrat, MD, Department of Internal Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; e-mail: tps68@georgetown.edu

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medication review before attributing villous atrophy to primary autoimmunity [6]. Existing cohorts illustrate that adult AIE often presents with severe malabsorption and may require intensive nutritional and immunosuppressive support [7]. However, serologies are adjunctive rather than definitive: anti-enterocyte and anti-goblet cell antibodies can be present in AIE but have imperfect specificity across other villous atrophy disorders [5]. Histopathology is heterogeneous but commonly shows villous blunting with inflammatory changes and crypt injury, and involvement beyond the duodenum is frequently described, suggesting a pan-enteric process in many patients [8].

Therapy is largely empiric, and typically combines immunosuppression with aggressive nutritional support. Corticosteroids are commonly used for induction, but sustained control often requires additional immunosuppressive therapy and nutritional rescue [7]. Small bowel-targeted strategies, such as open-capsule budesonide, have been reported as effective in selected cohorts after failure of conventional systemic therapy [9]. Despite step-up regimens, outcomes remain guarded in available series [5]. Other tertiary-center experiences similarly describe early steroid responsiveness with frequent relapse over longer follow up [10]. Given evolving diagnostic criteria, imperfect biomarkers, and an evidence base dominated by small series and case reports [3,4], comprehensive synthesis is essential to clarify diagnostic patterns, summarize reported therapies, and contextualize outcomes in adult AIE.

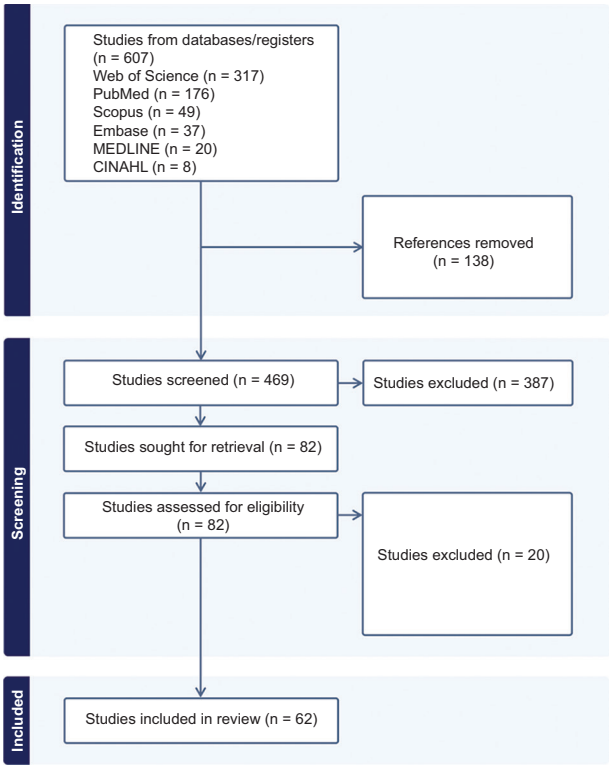

Figure 1 PRISMA flow diagram of study selection for the adult autoimmune enteropathy systematic review (1997-2025)

Materials and methods

Search strategy and study selection

Following the PRISMA 2020 reporting guidelines [11], we conducted a systematic review of published reports describing AIE in adults. We searched Web of Science, PubMed, Scopus, Embase, MEDLINE, and CINAHL from database inception through 4 January 2026 using keywords and controlled vocabulary related to AIE (e.g., "autoimmune enteropathy," "autoimmune enteritis," "anti-enterocyte antibody," "anti-goblet cell antibody"). Records were imported into Covidence (Veritas Health Innovation, Melbourne, Australia) for deduplication and screening; 2 reviewers independently screened titles/abstracts and full texts, with disagreements resolved by consensus. Study selection is summarized in the PRISMA flow diagram (Fig. 1). Data extraction was performed independently by 2 reviewers using a standardized form; discrepancies were resolved by consensus. Inter-rater agreement was assessed using Cohen's kappa (titles/abstracts κ=0.71; full text κ=0.68). The completed PRISMA 2020 checklist is provided as Supplementary Table 1.

Eligibility criteria

We included human case reports, case series and observational studies reporting original clinical data on adult autoimmune enteropathy (age ≥18 years or described as adult/late-onset by the original authors). Mixed pediatric/adult series were included only when adult cases were extractable; pediatric-only series and non-original publications (reviews, editorials) were excluded. Conference abstracts and letters were included only when sufficient patient-level clinical information was available for extraction. No language restrictions were imposed; when needed, non-English publications were translated for screening and data extraction.

Data extraction and synthesis

The review protocol was developed a priori; however, it was not prospectively registered (e.g., PROSPERO). Using a standardized extraction form, we captured publication-level variables (year, journal, country/region, report type) and, when available, case-level variables (demographics, symptoms, autoimmune comorbidities, diagnostic evaluation including endoscopy, histology and serology, treatments, nutritional

[a]Department of Internal Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA (Thomas Stirrat); [b]Georgetown University School of Medicine, Washington, DC, USA (Priyanka Solanky, Varat Ransibrahmanakul, Lovedeep Singh, Olivia Allen); [c]Medical College of Wisconsin, Milwaukee, WI, USA (Michael Flatley); [d]Kentucky College of Osteopathic Medicine, Pikeville, KY, USA (Soham Apte); [e]Department of Gastroenterology, MedStar Georgetown University Hospital, Washington, DC, USA (Priyanka Kanth)

support, and outcomes). For multi-patient series, individual-level data were extracted when available; otherwise, series-level aggregates were retained. Missing data were recorded as not reported and not imputed; all summaries use variable-specific denominators. To standardize narrative reporting, initial alternative diagnoses were categorized a priori (celiac/refractory celiac disease; IBD/microscopic colitis; infectious; medication-related; immunodeficiency-related; other). Villous atrophy severity was recorded only when explicitly graded (partial/subtotal/total). Serologies (tissue transglutaminase [tTG] IgA, endomysial antibody [EMA], and anti-enterocyte/anti-goblet cell antibodies, when reported) were coded as positive, negative, or indeterminate/unclassifiable when polarity could not be assigned. Treatments were coded as used versus not used when explicitly stated, and were summarized as non-mutually exclusive. Given the heterogeneity and the predominance of case reports/series, we performed descriptive analyses only (n [%], median [range]) and did not conduct a meta-analysis or formal risk-of-bias assessment; instead, we quantified reporting completeness across key variables (Supplementary Fig. 1) For larger case series or cohorts, we extracted individual cases when sufficient patient-level detail was provided. To avoid double counting across overlapping reports/series, we performed deduplication using available identifiers (age/sex, location, comorbidities, timeframe, and distinctive clinical/histologic features), retaining the most complete report when overlap was suspected. Analyses and figures were generated in Python (pandas, matplotlib).

Table 1 Study and patient characteristics of reported adult autoimmune enteropathy (AIE) cases included in this review (see Supplementary Table 2 for full list of included publications) [1-10,12-71]

Characteristic	Summary
Number of studies	n=55
Publication year	1997-2025
Geographic region	North America: 23 (41.8%); Europe: 20 (36.4%); Asia: 6 (10.9%); Not reported/unclear: 5 (9.1%); Oceania: 1 (1.8%)
Patient age, years	Median 49 (range 18-82)
Patient sex	Female: 70 (58.8%); Male: 49 (41.2%)
Patients per study	1: 50 (90.9%); 8: 1 (1.8%); 13: 1 (1.8%); 15: 1 (1.8%); 16: 1 (1.8%); 17: 1 (1.8%)
Study design	Case report: 46 (83.6%); Case series: 5 (9.1%); Retrospective study: 2 (3.6%); Case report (with literature review): 1 (1.8%); Retrospective cohort study: 1 (1.8%)
Publication type	Full text: 44 (80.0%); Abstract: 6 (10.9%); Letter: 3 (5.5%); Clinical observation: 1 (1.8%); Not reported: 1 (1.8%)

Publications (n=55; 1997-2025) including 119 patient cases are summarized as n (%) or median (range) using variable-specific denominators

Results

Study yield and reporting

We identified 55 publications (1997-2025) describing AIE, comprising 119 unique adult cases (Table 1; Fig. 1); publication frequency increased in more recent years. Geographic origin was most commonly North America (23/55, 41.8%) and Europe (20/55, 36.4%), with fewer reports from Asia (6/55, 10.9%) and Oceania (1/55, 1.8%); the region was not reported or unclear in 5/55 (9.1%). Reporting completeness varied substantially across variables (Supplementary Fig. 1): histopathology and treatment exposures were more consistently described than laboratory and micronutrient measures, limiting uniform quantitative synthesis in several domains. A complete study list with extracted adult case counts is provided in Supplementary Table 2, and case-level extracted variables are provided in Supplementary Tables 3A and 3B.

Patient characteristics and presentation

Median age was 49 years (range 18-82) among cases where age was reported (119/119, 100%). Sex was also available for all cases (119/119, 100%), with 70/119 (58.8%) being female (Table 1). Diarrhea was nearly universally documented (118/119, 99.2%) and, when reported, was present in 118/118 (100%). Other gastrointestinal symptoms were less consistently reported, but were common when described, including abdominal pain (reported in 44/119, 37.0%; present in 29/44, 65.9%), nausea (reported in 14/119, 11.8%; present in 12/14, 85.7%), vomiting (reported in 31/119, 26.1%; present in 26/31, 83.9%), and nocturnal diarrhea (reported in 4/119, 3.4%; present in 4/4, 100%). Markers of severity were infrequently described, including dehydration (reported in 7/119, 5.9%; present in 7/7, 100%) and hypotension (reported in 6/119, 5.0%; present in 4/6, 66.7%). Markers of malnutrition were common when quantifiable: numeric weight loss was extractable in 26/119 (21.8%) cases, with a median loss of 18 kg (interquartile range [IQR] 10-28; range 2-70).

Basis for diagnosis across reports

The diagnosis of AIE was clinicopathologic and heterogeneous across published reports, with no single feature reported universally. Instead, authors most commonly attributed the diagnosis to convergence of: (i) chronic severe diarrhea and/or malabsorption; (ii) small-bowel villous injury on histology; (iii) exclusion of common mimickers—particularly celiac disease (including refractory celiac disease), infection, medication-related enteropathy and immunodeficiency-related etiologies; and (iv) supportive immune features such as anti-enterocyte/anti-goblet cell antibodies and/or epithelial lineage abnormalities (goblet and Paneth cell loss). In our extracted dataset, diarrhea and small-bowel involvement were the most consistently documented diagnostic anchors, whereas "supportive" immune features and exclusionary testing were

variably reported across cases. However, individual "supportive" elements were variably reported and were rarely definitive in isolation: villous atrophy severity was graded in 18/55 publications, epithelial lineage findings were inconsistently assessed (goblet cell loss reported in 39/119 [32.8%], Paneth cell loss reported in 26/119 [21.8%]), and celiac serologies were variably reported and often negative when available: tTG IgA (n=84) was negative in 39/84, positive in 6/84, and unclear in 39/84, while EMA (n=74) was negative in 21/74 and unclear in 53/74 (positive 0/74). Anti-enterocyte antibody (AEA) testing was reported most often (n=107), with 25 positive, 20 negative and 62 unclear results, underscoring that most diagnoses relied on overall clinicopathologic pattern recognition plus exclusion of alternatives, rather than a single universal marker. Case-level documentation of each diagnostic element is summarized in Supplementary Table 3A.

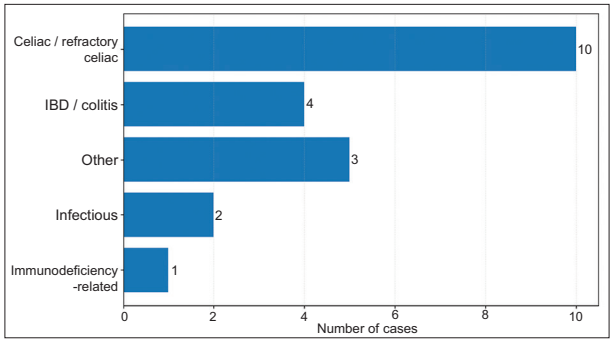

Figure 2 Initial misdiagnosis categories before recognition of AIE. Bars show counts of cases with an explicitly reported initial alternative diagnosis (n=22/119), most commonly celiac disease/refractory celiac disease, IBD/colitis, and infectious etiologies
AIE, adult autoimmune enteropathy; IBD, inflammatory bowel disease

Diagnostic evaluation and disease phenotype

AIE most consistently involved the small bowel; anatomic extent was explicitly documented in 102/119 (85.7%) cases, and among these small-bowel involvement was universal (102/102, 100%). Extra-duodenal evaluation was common: colonoscopy performance was explicitly reported in 52/119 (43.7%) cases and was performed in 52/52 (100%) of them. Colonic involvement was explicitly documented in 52/119 (43.7%) cases and, when reported, was frequent (37/52, 71.2%).

Laboratory data were variably reported; among cases with numeric values extractable and unit-normalized, median albumin was 2.80 g/dL (IQR 1.95-3.55; reported in 23/119, 19.3%) and median hemoglobin was 10.3 g/dL (IQR 9.5-17.9; reported in 17/119, 14.3%), consistent with protein-losing enteropathy/malabsorption and chronic inflammatory illness. Infectious evaluation was inconsistently documented but generally unrevealing: stool culture results were reported in 22/119 (18.5%) cases and were negative in 17/22 (77.3%). Out of the remaining 5 cases, 4 culture results were unspecified or unclear, while 1 report noted *Candida albicans* on stool culture, though this finding was isolated and of uncertain clinical significance.

An initial diagnostic impression prior to recognition of AIE was explicitly described in 22/119 (18.5%) cases (Fig. 2), most often celiac disease/refractory celiac disease (10/22, 45.5%), followed by "other" diagnoses (5/22, 22.7%), IBD/colitis (4/22, 18.2%), infectious etiologies (2/22, 9.1%), and immunodeficiency-related diagnoses (1/22, 4.5%).

Villous atrophy severity (partial/subtotal/total) was reported in 18/55 (32.7%) publications, corresponding to 46/119 (38.7%) cases with graded severity available, and when graded uniformly reflected villous injury (Fig. 3A). Epithelial-lineage abnormalities were also common when specifically documented: goblet cell loss was reported in 39/119 (32.8%) cases and present in 31/39 (79.5%), while Paneth cell loss was reported in 26/119 (21.8%) cases and present in 17/26 (65.4%).

Celiac serologies were variably reported but were usually negative when available (Fig. 3B). tTG IgA results were reported in n=84 tests/cases, with 39 negative, 6 positive, and 39 unclear. EMA results were reported in n=74, with 21 negative, 0 positive, and 53 unclear. AEA testing was reported most often (Fig. 3C), with n=107 total results: 25 positive, 20 negative, and 62 unclear. Together, the combination of villous injury, frequent initial labeling as celiac disease or IBD/colitis, predominantly negative celiac serologies, and frequent AEA positivity supports a recurring pattern of AIE presenting as a celiac/IBD mimic (Figs. 2 and 3).

Reported treatments (Fig. 4) were dominated by systemic steroids (78/80) and parenteral nutrition (28/28) among cases where use/non-use was explicitly documented; other immunosuppressive/biologic exposures were less common (e.g., azathioprine 18/30; any anti- tumor necrosis factor [TNF] 16/31; infliximab 15/30; tacrolimus 8/23; cyclosporine 8/23; intravenous immunoglobulin 5/20; vedolizumab 4/5; mycophenolate 2/3; ustekinumab 2/3).

Exploratory analyses assessing whether documentation of an initial misdiagnosis correlated with symptom duration or adverse outcomes were limited by sparse, non-uniform reporting.

Time course, comorbid immune phenotypes and follow up/response

The duration of symptoms prior to diagnosis was reported in 43/119 (36.1%) cases; among these, median symptom duration was 6.0 months (IQR 2.5-24.0; range ~0.9-240 months), and most reported courses were ≤12 months (28/43, 65.1%). Follow up was reported in 108/119 (90.8%), and numeric follow-up duration was extractable in 75/119 (63.0%), where the median follow up was 20.5 months (IQR 13.0-47.2; range 1-420 months). Autoimmune comorbidity was commonly documented, but not uniformly reported: autoimmune comorbidity status was reported in 57/119 (47.9%) cases and, when reported, was present in 48/57 (84.2%). Immunodeficiency status was reported in 58/119 (48.7%) cases and was present in 18/58 (31.0%). Thymoma status was reported in 10/119 (8.4%) cases and, when reported, was present in 7/10 (70.0%). When response timing was reported, improvement could be rapid: time to clinical response was extractable in 13/119 (10.9%)

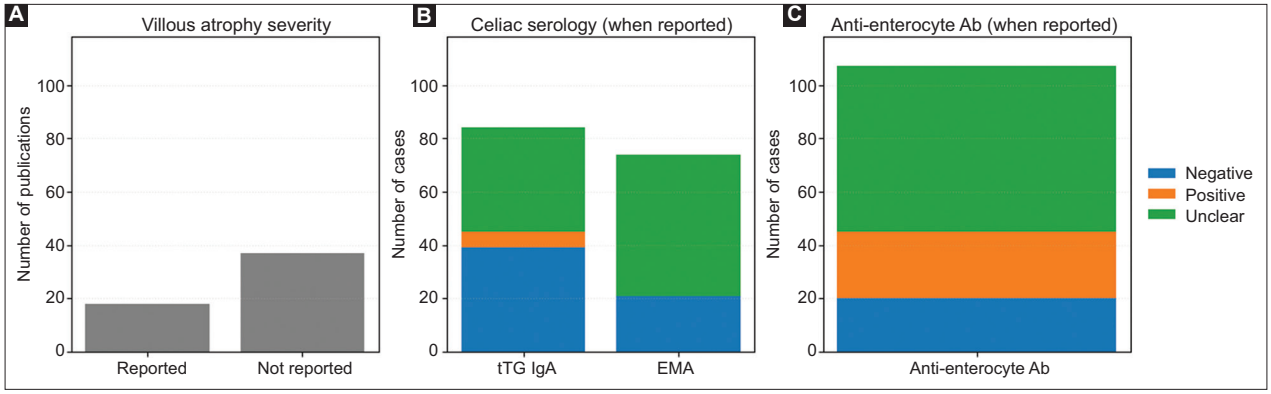

Figure 3 Histology and serology patterns supporting adult autoimmune enteropathy as a celiac/IBD mimic. (A) Reporting of villous atrophy severity (partial/subtotal/total) across included publications (reported in 18/55 publications). (B) Celiac serology results—tTG IgA and endomysial antibody (EMA)—and (C) anti-enterocyte antibody (AEA) results among cases with reported testing (excluding tests explicitly noted as not performed/not tested), categorized as Negative, Positive, or Unclear. Panel B: tTG IgA (n=84; Negative 39, Positive 6, Unclear 39) and EMA (n=74; Negative 21, Positive 0, Unclear 53). Panel C: AEA (n=107; Negative 20, Positive 25, Unclear 62). Shared legend applies to panels B & C
tTG, tissue transglutaminase; EMA, endomysial antibody; AEA, anti-enterocyte antibody; IBD, inflammatory bowel disease

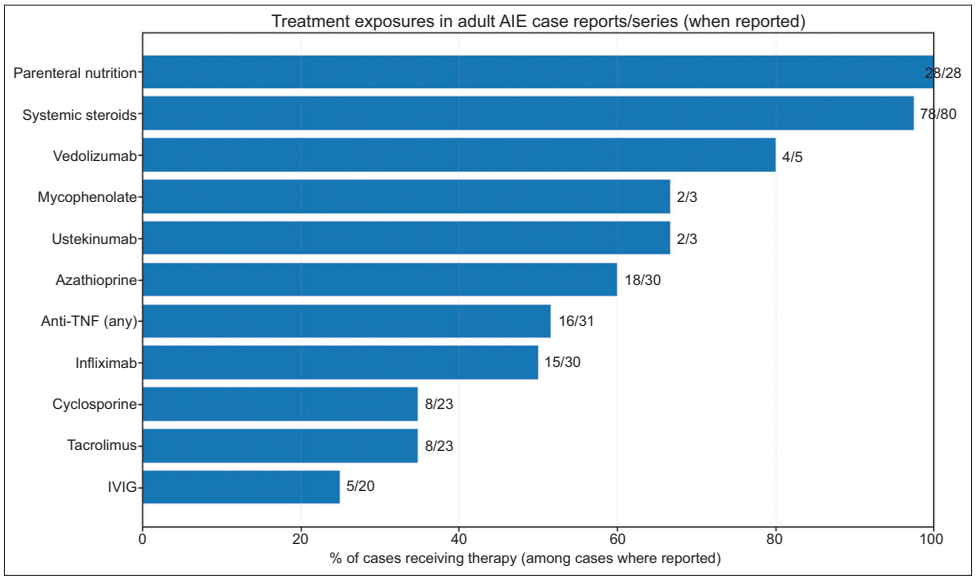

Figure 4 Reported treatment exposures in AIE. Bars show the percentage of cases receiving each therapy among cases with explicit documentation of use versus non-use reporting; values at the end of each bar indicate the number treated over the number with available reporting (n/N). Therapies are not mutually exclusive
AIE, adult autoimmune enteropathy; anti-TNF, anti-tumor necrosis factor; IVIG, intravenous immunoglobulin

cases, with a median of 14 days (IQR 5-30.4; range 2-365 days). Follow-up endoscopy was described in 21/119 (17.6%), though histologic response reporting remained inconsistent.

Treatment patterns

Treatment reporting was variable and typically non-mutually exclusive. Systemic corticosteroid exposure was explicitly documented in 80/119 (67.2%) cases and, when documented, systemic corticosteroids were used in 78/80 (97.5%) (Fig. 4). Steroid-sparing immunosuppressants were commonly used when exposure was explicitly reported, including azathioprine (reported in 30/119, 25.2%; used in 18/30, 60.0%) and calcineurin inhibitors (tacrolimus reported in 23/119, 19.3%; used in 8/23, 34.8%; cyclosporine reported in 23/119, 19.3%; used in 8/23, 34.8%). Biologic therapy was also reported, including anti-TNF therapy (infliximab and/or adalimumab) in 31/119 (26.1%) cases with explicit exposure documentation, where anti-TNF therapy was used in 16/31 (51.6%) (infliximab used in 15/30, 50.0%). Newer biologics (e.g., vedolizumab, ustekinumab) were reported in small numbers (vedolizumab reported in 5/119, 4.2%; used in 4/5, 80.0%; ustekinumab reported in 3/119, 2.5%; used in 2/3, 66.7%). Nutritional support was prominent when explicitly discussed: parenteral nutrition use/non-use was reported in 28/119 (23.5%) cases and,

when reported, parenteral nutrition was used in 28/28 (100%) (Fig. 4). Overall, frequent escalation beyond corticosteroids suggests that published cases often represent steroid-dependent or steroid-refractory disease. Case-level treatment exposures are summarized in Supplementary Table 3B.

Outcomes

Outcome reporting was heterogeneous and often narrative. Relapse status was reported in 27/119 (22.7%) cases; among these, relapse occurred in 17/27 (63.0%). Mortality status was reported in 18/119 (15.1%) cases; among these, death occurred in 7/18 (38.9%) (Supplementary Fig. 2). Among cases where the cause of death was given, fatal outcomes most often reflected infectious complications in the setting of severe disease and immunosuppression (5/7, 71.4% infection/sepsis-related). However, these proportions reflect only cases with explicit outcome reporting, and therefore should not be interpreted as population-level rates. Relapse, mortality, and follow up are summarized in Supplementary Table 3B.

Discussion

In this systematic review of 55 publications describing 119 adult cases, AIE consistently presented with severe watery diarrhea and profound malabsorption, and was frequently first labeled as celiac disease/refractory celiac disease or IBD, reinforcing AIE as a high-morbidity "celiac/IBD mimic" within the broader syndrome of seronegative villous atrophy [3,5,7,8,10]. Across the literature, reporting was heterogeneous and often incomplete, which limits uniform quantitative synthesis but also highlights where the field most needs standardization (Supplementary Fig. 1; Supplementary Tables 2 and 3).

Our case-level synthesis aligns with and extends prior adult AIE cohorts and larger series that form the main comparative reference points in this rare disease (Supplementary Table 4). The Mayo Clinic experience (Akram *et al* [7]) and a subsequent European tertiary-center cohort (van Wanrooij *et al* [5]) similarly emphasize a clinicopathologic diagnosis anchored by severe diarrhea/malabsorption, with villous injury and systematic exclusion of mimickers, in which supportive tests were variably informative across patients. In cohorts with more standardized diagnostic workups, interpretable celiac serologies were consistently negative (e.g., uniformly negative interpretable tTG/EMA in the European cohort), and epithelial-lineage abnormalities (goblet/Paneth depletion) were more frequently documented; in contrast, pathology-focused series and some larger reports contributed substantial case numbers, but did not uniformly report serologies, antibody testing or graded villous atrophy in extractable form. More recent single-center cohorts reinforce the geographic breadth, and suggest that relapsing or treatment-dependent courses are common, but they also underscore persistent variability in how immune markers are measured and reported. By aggregating scattered adult AIE reports through 2025 and pairing transparent case-level extraction (Supplementary Tables 2 and 3) with cohort comparisons (Supplementary Table 4), our review strengthens the clinical takeaway that no single marker is sufficient, and adult AIE remains an integrated clinicopathologic diagnosis situated within modern seronegative enteropathy frameworks. By extracting case-level diagnostic trajectories, we were able to quantify features that are often mentioned anecdotally but rarely summarized across adult AIE, most notably the initial misdiagnosis patterns preceding recognition of AIE (Fig. 2).

Evaluation should follow contemporary seronegative enteropathy frameworks: confirm gluten exposure, exclude celiac disease (including IgA deficiency and seronegative celiac disease), and systematically assess medications, infections, immunodeficiency and lymphoproliferative disease before diagnosing AIE [12-18]. Anti-enterocyte/anti-goblet cell antibodies were often positive in the AIE literature, but imperfect specificity (including positivity in other villous atrophy disorders) supports their use as adjunctive rather than diagnostic tests [5,12]. We contextualize our case-level synthesis relative to major adult AIE cohorts/series in Supplementary Table 4. Practical clinicopathologic "red flags" include villous atrophy with negative/discordant celiac serology and nonresponse to dietary elimination, prominent crypt apoptosis with depletion of goblet/Paneth lineages, and frequent pan-enteric involvement across the upper and lower gastrointestinal tract [5,7,8,10,12]. Because sprue-like drug enteropathy, classically with olmesartan, can be clinically indistinguishable yet reversible, meticulous medication review remains essential before escalating immunosuppression [6,12].

Therapeutic evidence remains observational, but consistent themes emerge: systemic corticosteroids dominate induction, relapse/steroid dependence is common, and many patients require step-up to steroid-sparing immunosuppressants and/or biologics [5,7,10]. Open-capsule budesonide has shown high response rates after failure of conventional systemic therapy, and provides a pragmatic small bowel-targeted steroid-sparing option [9]. For multiple refractory disease, gut-selective therapy (e.g., vedolizumab) has been reported at the case level, but evidence is too limited to define optimal sequencing [19]. Given the links to immune dysregulation, baseline immunologic evaluation and consideration of checkpoint insufficiency syndromes (e.g., CTLA-4) are appropriate in severe, multisystem or refractory presentations [20]. The case report-dominated literature and inconsistent reporting constrain comparative inference, underscoring the need for standardized diagnostic criteria and multicenter registries aligned with emerging consensus frameworks for seronegative villous atrophy [12,17,18].

In conclusion, in this structured synthesis of AIE, we identified 55 publications (1997-2025) describing 119 cases, with the evidence base dominated by single-patient reports. Across reported cases, AIE most often presented with severe diarrhea and malabsorptive enteropathy with villous injury, and was frequently initially evaluated as celiac disease/refractory celiac disease or IBD. When testing was reported, celiac serologies were typically negative, while

anti-enterocyte antibodies were frequently positive, and epithelial-lineage abnormalities (goblet and Paneth cell loss) were common, supporting a recurring clinicopathologic pattern of AIE as a celiac/IBD mimic marked by histology-serology discordance.

Therapeutic approaches reflected high disease severity: systemic corticosteroids were used in 78/80 (97.5%) cases when exposure was explicitly reported, with frequent escalation to steroid-sparing immunosuppressants and biologics, and common reliance on parenteral nutrition. Outcomes were variably reported, and were subject to reporting and publication bias. Among the subset with explicit reporting, relapse occurred in 17/27 (63.0%) and death in 7/18 (38.9%); however, these proportions should not be interpreted as population-level rates. Moving the field forward will require standardized reporting of diagnostic testing, histopathologic features, treatment sequencing and outcomes, alongside multicenter prospective cohorts/registries to define durable, steroid-sparing strategies and improve long-term disease control.

Summary Box

What is already known:

- Autoimmune enteropathy (AIE) is a rare immune-mediated cause of chronic watery diarrhea, malabsorption, and non-celiac villous atrophy
- Adult AIE overlaps clinically and histologically with celiac disease, refractory celiac disease, inflammatory bowel disease (IBD), medication-related enteropathy, immunodeficiency-associated enteropathy, and other causes of seronegative villous atrophy
- Anti-enterocyte and anti-goblet cell antibodies, celiac serologies and epithelial-lineage abnormalities can support the diagnosis, but none is sufficiently sensitive or specific as a standalone marker
- Treatment evidence is largely observational, and commonly involves corticosteroids, steroid-sparing immunosuppression/biologics and nutritional support in severe cases

What the new findings are:

- This systematic review identified 55 publications from 1997-2025 describing 119 unique adult AIE cases, with reporting dominated by case reports and small series
- Diarrhea was nearly universal when reported, and small-bowel involvement was universal among cases with explicit anatomic documentation
- Initial alternative diagnoses were often celiac disease/refractory celiac disease or IBD/colitis, supporting adult AIE as a high-morbidity celiac/IBD mimic with serology-histology discordance
- Published management frequently used systemic corticosteroids, escalation to steroid-sparing agents/biologics and parenteral nutrition; relapse and mortality proportions should be interpreted cautiously because outcome reporting was sparse and heterogeneous

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Supplementary material

Supplementary Table 1 PRISMA 2020 checklist

Section	Item	Checklist item	Location in manuscript
Title	1	Identify the report as a systematic review	Title page
Abstract	2	Provide a structured summary of background, objectives, eligibility criteria, sources, methods, results, limitations and implications	Abstract
Introduction	3	Describe the rationale for the review in the context of existing knowledge	Introduction
Introduction	4	State the review objectives or questions	Introduction
Methods	5	Specify the eligibility criteria and how studies were grouped for synthesis	Eligibility criteria
Methods	6	Specify all information sources, including databases, and the date of last search	Search strategy and study selection
Methods	7	Present the full search strategy or sufficient detail for reproducibility	Search strategy and study selection
Methods	8	Describe how records and reports were screened and selected	Search strategy and study selection
Methods	9	Describe the data collection process and reviewer procedures	Search strategy and study selection; Data extraction and synthesis
Methods	10a	List and define all outcomes for which data were sought	Data extraction and synthesis
Methods	10b	List and define other variables for which data were sought	Data extraction and synthesis
Methods	11	Describe methods used to assess risk of bias in included studies	Not applicable; formal risk-of-bias assessment was not performed because evidence consisted mainly of case reports/series
Methods	12	Specify effect measures used for each outcome	Not applicable; descriptive synthesis only
Methods	13a	Describe processes used to decide which studies were eligible for each synthesis	Data extraction and synthesis
Methods	13b	Describe data preparation, transformations or assumptions before synthesis	Data extraction and synthesis
Methods	13c	Describe methods used to tabulate or visually display results	Data extraction and synthesis; Figures 1-4; Supplementary Figure 1 and 2
Methods	13d	Describe synthesis methods used	Data extraction and synthesis
Methods	13e	Describe methods used to explore possible causes of heterogeneity	Data extraction and synthesis; no meta-analysis was performed
Methods	13f	Describe sensitivity analyses used to assess robustness	Not applicable; no sensitivity analyses were performed
Methods	14	Describe methods used to assess risk of bias due to missing results in a synthesis	Not applicable; no meta-analysis was performed
Methods	15	Describe methods used to assess certainty or confidence in the body of evidence	Not applicable; no certainty assessment was performed
Results	16a	Describe results of the search and selection process, ideally using a flow diagram	Results; Figure 1
Results	16b	For updated reviews, present previous and new studies separately	Not applicable; this was not an update of a prior review
Results	17	Cite each included study and present its characteristics	Table 1; Supplementary Table 1
Results	18	Present risk-of-bias assessments for included studies	Not applicable; formal risk-of-bias assessment was not performed
Results	19	Present results for all outcomes for each study	Results; Supplementary Tables 2A and 2B
Results	20a	Provide summary characteristics and results for each synthesis	Results; Tables 1 and Supplementary Tables 1-3; Figures 2-4

(Contd...)

Supplementary Table 1 *(Continued)*

Section	Item	Checklist item	Location in manuscript
Results	20b	Present results of statistical syntheses	Not applicable; no meta-analysis was performed
Results	20c	Present results of investigations of possible causes of heterogeneity	Not applicable; descriptive synthesis only
Results	20d	Present results of sensitivity analyses	Not applicable; no sensitivity analyses were performed
Results	21	Present assessments of risk of bias due to missing results	Not applicable; no meta-analysis was performed
Results	22	Present certainty or confidence assessments for each outcome	Not applicable; no certainty assessment was performed
Discussion	23a	Provide a general interpretation of results in context	Discussion
Discussion	23b	Discuss limitations of the included evidence	Discussion; Conclusion
Discussion	23c	Discuss limitations of the review process	Discussion; Conclusion
Discussion	23d	Discuss implications for practice, policy and future research	Discussion; Conclusion
Other information	24a	Provide registration information or state that the review was not registered	Data extraction and synthesis
Other information	24b	Indicate where the review protocol can be accessed	Data extraction and synthesis
Other information	24c	Describe and explain amendments to registration or protocol information	Not applicable; protocol was not prospectively registered
Other information	25	Describe sources of support and the role of funders or sponsors	Not reported
Other information	26	Declare competing interests of review authors	Title page
Other information	27	Report availability of data, code and other materials	Supplementary Tables 1-3; additional data available within extracted tables

Checklist adapted from Page *et al* [11]. Items marked not applicable reflect that this review used descriptive synthesis without meta-analysis or formal certainty/risk-of-bias assessment

Supplementary Table 2 Included adult autoimmune enteropathy (AIE) publications and extracted adult case counts

Study (first author, year - title - journal)	Type	n
Corazza 1997 — Autoimmune enteropathy and villous atrophy in adults (The Lancet) [2]	FT	1
Mitomi 1998 — Autoimmune Enteropathy with Severe Atrophic Gastritis and Colitis in an Adult: Proposal of a Generalized Autoimmune Disorder of the Alimentary Tract (Scand J Gastroenterol) [21]	FT	1
Mais 1999 — Thymoma-Associated Autoimmune Enteropathy A Report of Two Cases (Am J Clin Pathol) [22]	FT	1
Rogahn 1999 — Autoimmune enteropathy with goblet-cell antibodies (Journal of the Royal Society of Medicine) [23]	FT	1
Casis 2002 — Autoimmune enteropathy in an adult with autoimmune multisystemic involvement (Scandinavian Journal of Gastroenterology) [24]	FT	1
Carroccio 2003 — Autoimmune Enteropathy and Colitis in an Adult Patient (Digestive Diseases and Sciences) [25]	FT	1
Daum 2003 — Adult Autoimmune Enteropathy Treated Successfully with Tacrolimus (Digestion) [26]	FT	1
Ashley 2004 — TREATMENT OF ADULT ONSET AUTOIMMUNE ENTEROPATHY WITH TACROLIMUS (FK506) (American Journal of Gastroenterology) [27]	Abs	1
Elwing 2005 — Adult-Onset Autoimmune Enteropathy in the Setting of Thymoma Successfully Treated with Infliximab (Digestive Diseases and Sciences) [28]	FT	1
von Hahn 2005 — Management of Severe Refractory Adult Autoimmune Enteropathy with Infliximab and Tacrolimus (Digestion) [29]	FT	1
Khalidi 2006 — Enteropathy with loss of enteroendocrine and Paneth cells in a patient with immune dysregulation: a case of adult autoimmune enteropathy (Human Pathology) [30]	FT	1

(Contd...)

Supplementary Table 2 *(Continued)*

Study (first author, year - title - journal)	Type	n
Akram 2007 — Adult Autoimmune Enteropathy: Mayo Clinic Rochester Experience (Clinical Gastroenterology and Hepatology) [7]	FT	15
Ranta 2010 — Cerebral venous thrombosis in autoimmune enteropathy (The New Zealand Medical Journal) [32]	FT	1
Pérez 2010 — Enteropatía autoinmune en un paciente adulto (Gastroenterología y Hepatología) [31]	ObsClin	1
Bishu 2011 — Autoimmune enteropathy with a CD8+ CD7- T-cell small bowel intraepithelial lymphocytosis: case report and literature review (BMC Gastroenterology) [33]	FT	1
Society of Hospital Medicine 2012 — Not Just Another Case of Diarrhea in the Hospital: Adult Autoimmune Enteropathy (Journal of Hospital Medicine, Volume 7, Suppl 2.) [36]	Abs	1
Ciccocioppo 2012 — Mesenchymal Stromal Cell Infusions as Rescue Therapy for Corticosteroid-Refractory Adult Autoimmune Enteropathy (Mayo Clin Proc.) [35]	FT	1
Chuang 2013 — Adult-onset Autoimmune Enteropathy Managed with Infliximab and Azathioprine (The American Journal of Gastroenterology) [37]	Abs	1
Xu 2014 — Glutamine-Supplemented Parenteral Nutrition and Probiotics in Four Adult Autoimmune Enteropathy Patients (Gut and Liver) [38]	FT	1
Masia 2014 — Gastrointestinal biopsy findings of autoimmune enteropathy: a review of 25 cases (Am J Surg Pathol) [8]	FT	8
Klinger 2015 — Adult Autoimmune Enteropathy Involving Small Bowel and Colon (The American Journal of Gastroenterology) [40]	Abs	1
Fidias 2015 — Case 31-2015 — A 29-Year-Old Man with Thymoma, Diarrhea, and Weight Loss (N Engl J Med) [39]	FT	1
Riquelme 2015 — Thymoma-associated chronic diarrhea: A case of autoimmune enteropathy (Cancer Treatment Communications) [41]	FT	1
Depince-Berger 2016 — A Difficult and Rare Diagnosis of Autoimmune Enteropathy in a Patient Affected by Down Syndrome (J Clin Immunol) [42]	Let	1
Hasan 2016 — Diffuse Autoimmune Enteropathy and Colopathy in an Adult Patient Successfully Treated With Adalimumab and a Review of the Literature (American Journal of Therapeutics) [43]	FT	1
Lie 2017 — Adult autoimmune enteropathy presenting initially with acquired Acrodermatitis Enteropathica: a case report (BMC Dermatology) [44]	FT	1
McCabe 2017 — Seronegative Adult Autoimmune Enteropathy in a Male Traveler (ACG Case Reports Journal) [45]	FT	1
Salas Antón 2018 — Adult Autoimmune Enteropathy and Colitis: A Challenge Successfully Treated With Adalimumab (Inflammatory Bowel Diseases) [47]	Let	1
Rodriguez 2018 — Autoimmune Enteropathy in an Ulcerative Colitis Patient (ACG Case Reports Journal) [48]	FT	1
Ciccocioppo 2018 — Intestinal T-cell lymphoma with enteropathy-associated T-cell lymphoma-like features arising in the setting of adult autoimmune enteropathy (Hematological Oncology) [46]	FT	1
Trivedi 2019 — Using Adalimumab to Treat Autoimmune Enteropathy (ACG Case Reports Journal) [51]	FT	1
Lundholm 2019 — Seronegative Adult Autoimmune Enteropathy in a Patient With Rheumatoid Arthritis (ACG Case Rep J) [50]	FT	1
Chetty 2019 — Adult-onset autoimmune-type enteropathy: potential relationship to an adverse drug reaction (BMJ Open Gastro) [49]	FT	1
Villanacci 2019 — Clinical manifestations and gastrointestinal pathology in 40 patients with autoimmune enteropathy (Clinical Immunology) [52]	FT	17
Beck 2020 — Die Autoimmunenteropathie beim Erwachsenen. Eine seltene und schwierige, aber relevante Differenzialdiagnose der chronischen Diarrhö (Der Pathologe) [53]	FT	1
Soma 2020 — Isolated Intestine Transplantation for Autoimmune Enteropathy: A Case Report (Transplantation Proceedings) [55]	NR	1
Chong 2021 — Seronegative autoimmune enteropathy with duodenal sparing and colonic clues in an adult female (Clinical Journal of Gastroenterology) [56]	FT	1
Iaquinto 2021 — Adult autoimmune enteropathy in autoimmune hepatitis patient. Case report and literature review (Clinics and Research in Hepatology and Gastroenterology) [58]	FT	1
Scheid 2021 — Successful Treatment of Refractory Autoimmune Enteropathy With Ustekinumab (ACG Case Reports Journal) [59]	FT	1
Zhou 2021 — Autoimmune enteropathy and primary biliary cholangitis after proctocolectomy for ulcerative colitis: A case report and review of the literature (World Journal of Gastroenterology) [60]	FT	1

(Contd...)

Supplementary Table 2 *(Continued)*

Study (first author, year - title - journal)	Type	n
van Wanrooij 2021 — Adult-Onset Autoimmune Enteropathy in an European Tertiary Referral Center (Clinical and Translational Gastroenterology) [5]	FT	13
Du 2021 — Case Report: MDM4 Amplified in a Thymoma Patient With Autoimmune Enteropathy and Myocarditis (Frontiers in Endocrinology) [57]	FT	1
Colizzo 2022 — Case 29-2022: A 33-Year-Old Man with Chronic Diarrhea and Autoimmune Enteropathy (N Engl J Med) [61]	FT	1
Carvalho 2023 — Autoimmune Enteropathy: A Rare Cause of Chronic Diarrhea in an Adult Patient (ACG Case Reports Journal) [63]	FT	1
Amer 2023 — A Combination Therapy in a Rare Case of Adult-Onset Autoimmune Enteropathy (Cureus) [62]	FT	1
Correia 2023 — A Rare Case of Autoimmune Enteropathy Associated with Autoimmune Hepatitis (J Gastrointestin Liver Dis) [64]	FT	1
Xu 2023 — Autoimmune enteropathy complicated with primary biliary cholangitis (Rev Esp Enferm Dig) [66]	Let	1
Lorentsen 2023 — Adult-Onset Autoimmune Enteropathy: A Case Report (Cureus) [65]	FT	1
Patel 2024 — A Rare Case of Autoimmune Enteropathy After Thymectomy (Cureus) [68]	FT	1
Giblen 2024 — Adult-Onset Autoimmune Enteropathy Mimicking Disaccharidase Deficiency (Gastroenterology Research) [67]	FT	1
Li 2024 — Clinical manifestations, diagnosis and long-term prognosis of adult autoimmune enteropathy: Experience from Peking Union Medical College Hospital (World Journal of Gastroenterology) [10]	FT	16
Gerqari 2025 — Adult Autoimmune Enteropathy and Acquired Acrodermatitis Enteropathica: A Rare Case Report (International Journal of Biomedicine) [70]	FT	1
Chlorakis 2025 — A Rare Case of Autoimmune Enteropathy Associated With Lambert-Eaton Myasthenic Syndrome and a Literature Review (Cureus) [69]	FT	1
Isaac-Coss 2025 — Vedolizumab-Induced Remission in Adult-Onset Autoimmune Enteropathy Complicated by Fibrotic Stricture (The American Journal of Gastroenterology) [71]	Abs	1
Lei NR — A CASE OF ADULT AUTOIMMUNE ENTEROPATHY AND PRIMARY SCLEROSING CHOLANGITIS (Not reported.) [54]	Abs	1

Type - FT full text; Abs abstract; Let letter; ObsClin clinical observation; NR not reported. n = unique adult cases extracted from each publication

Supplementary Table 3A Case-level diagnostic features and basis for diagnosis across included adult autoimmune enteropathy (AIE) cases

Case	Study [ref.]	Ctry	Age (years)	Sex	SB/ Col	VA	Gb/Pa	tTG/ EMA	AEA/ AGCA	MisDx	Criteria
1	Society of Hospital Medicine 2012 [36]	NR	48	F	+/+	T	./.	-/.	-/.	Inf	+
2	von Hahn 2005 [29]	DEU	19	M	+/-	T	./.	-/-	+/.	IBD/CeD	+
3	Xu 2014 [38]	CHN	28	F	+/.	P-T	./.	./.	./.	.	+
4	Klinger 2015 [40]	USA	64	F	+/+	U	+/+	./.	+/.	IBD	+
5	Lei NR [54]	CAN	31	M	+/+	.	./.	./.	./.	IBD	+
6	Mitomi 1998 [21]	JPN	59	M	+/+	T	./.	./.	NT/.	.	+
7	Ranta 2010 [32]	NZL	37	M	+/.	.	+/.	./.	+/.	Oth	+
8	Rogahn 1999 [23]	UK	19	F	+/+	.	+/.	./.	-/?	.	+
9	McCabe 2017 [45]	USA	45	M	+/+	T	+/.	./.	-/.	Inf	+
10	Soma 2020 [55]	USA	55	M	+/+	T	+/+	./.	-/-	IBD	+
11	Lundholm 2019 [50]	USA	75	F	+/-	U	+/.	1/.	-/.	Inf/Oth	+
12	Lorentsen 2023 [65]	DNK	82	F	+/+	U	./.	-/.	NT/.	.	+
13	Lie 2017 [44]	USA	41	F	+/.	.	./.	-/.	-/.	Oth	+
14	Iaquinto 2021 [58]	ITA	73	F	+/.	T	+/.	-/-	+/.	.	+
15	Mais 1999 [22]	USA	52	M	+/+	.	+/.	./.	+/.	.	+
16	Corazza 1997 [2]	ITA	38	F	+/.	T	./.	./-	-/.	.	+

(Contd...)

Supplementary Table 3A *(Continued)*

Case	Study [ref.]	Ctry	Age (years)	Sex	SB/ Col	VA	Gb/Pa	tTG/ EMA	AEA/ AGCA	MisDx	Criteria
17	Daum 2003 [26]	DEU	54	M	+/.	T	+/.	-/-	-/.	.	+
18	Du 2021 [57]	CHN	22	M	+/+	.	+/.	./.	./+	.	+
19	Zhou 2021 [60]	CHN	54	F	+/.	U	+/+	./.	./.	.	+
20	Scheid 2021 [59]	USA	75	M	+/.	.	+/+	./.	-/-	.	+
21	Fidias 2015 [39]	USA	29	M	+/+	U	+/+	./.	+/.	.	+
22	Gerqari 2025 [70]	XKX	81	M	./.	.	./.	./.	./.	.	.
23	Giblen 2024 [67]	USA	27	M	+/.	S	+/+	./.	NT/NT	Inf/Oth	+
24	Hasan 2016 [43]	USA	28	M	+/+	.	./.	./-	+/.	.	+
25	Carroccio 2003 [25]	ITA	50	F	+/+	P	./.	2.3/-	?/.	CeD/Oth	.
26	Carvalho 2023 [63]	PRT	73	F	+/-	U	./.	./.	-/.	.	+
27	Casis 2002 [24]	ESP	58	F	+/+	S	./.	./-	+/.	.	+
28	Chetty 2019 [49]	CAN	54	F	+/+	T	+/+	./.	./.	CeD	+
29	Chlorakis 2025 [69]	GRC	24	F	+/+	.	./.	4/-	NT/NT	Med	+
30	Trivedi 2019 [51]	NR	52	F	+/-	T	+/+	-/.	+/.	.	.
31	Ciccocioppo 2018 [46]	ITA	41	F	+/.	T	./.	+/-	+/.	CeD	+
32	Ciccocioppo 2012 [35]	ITA	61	F	+/-	U	./.	-/-	+/.	CeD	+
33	Colizzo 2022 [61]	USA	33	M	+/+	S	./.	-/.	+/.	.	+
34	Elwing 2005 [28]	USA	82	F	+/-	U	+/.	-/-	+/.	.	+
35	Bishu 2011 [33]	USA	28	F	+/.	T	-/.	-/.	-/.	CeD/Inf	+
36	Xu 2023 [66]	CHN	28	F	+/.	.	+/.	./.	./.	.	+
37	Correia 2023 [64]	PRT	74	F	+/.	T	./.	-/.	NT/NT	.	+
38	Chong 2021 [56]	USA	43	F	+/+	P	+/+	./.	-/.	ID	+
39	Depince-Berger 2016 [42]	FRA	24	F	+/+	T	+/.	111/-	-/+	CeD	+
40	Patel 2024 [68]	USA	66	M	+/.	P	./.	-/.	+/+	.	+
41	Khalidi 2006 [30]	CAN	21	M	+/.	T	+/+	-/-	./.	CeD	+
42	Amer 2023 [62]	USA/SAU	28	F	+/.	S	./.	?/.	?/.	.	+
43	Chuang 2013 [37]	USA	77	F	+/.	U	./.	-/.	+/.	.	+
44	Isaac-Coss 2025 [71]	NR	74	F	+/.	U	+/+	-/.	-/.	Inf	.
45	Beck 2020 [53]	DEU	26	F	+/+	T	+/+	./.	-/NT	CeD	+
46	Ashley 2004 [27]	USA	64	M	+/-	.	./.	./.	./.	.	.
47	Pérez 2010 [31]	ESP	63	M	+/.	T	./.	1/-	./.	.	+
48	Salas Antón 2018 [47]	ESP	37	F	+/+	.	./.	./.	-/+	.	+
49	Riquelme 2015 [41]	USA	35	M	+/.	.	+/.	./.	+/.	.	+
50	Rodriguez 2018 [48]	USA	54	F	+/.	P-T	-/-	-/.	?/+	IBD/Inf/Oth	.
51	Akram 2007 [7]	USA	61	F	+/.	.	./.	+/.	+/.	.	+
52	Akram 2007 [7]	USA	37	M	+/.	.	./.	-/.	+/.	.	+
53	Akram 2007 [7]	USA	75	M	+/+	.	./.	-/.	+/+	.	+
54	Akram 2007 [7]	USA	46	F	+/+	.	./.	+/.	+/+	.	+
55	Akram 2007 [7]	USA	42	F	+/+	.	./.	-/.	+/.	.	+
56	Akram 2007 [7]	USA	38	F	+/.	.	./.	+/.	+/.	.	+
57	Akram 2007 [7]	USA	76	F	+/.	.	./.	-/.	./+	.	+

(Contd...)

Supplementary Table 3A *(Continued)*

Case	Study [ref.]	Ctry	Age (years)	Sex	SB/ Col	VA	Gb/Pa	tTG/ EMA	AEA/ AGCA	MisDx	Criteria
58	Akram 2007 [7]	USA	55	M	+/+	.	./.	-/.	./+	.	+
59	Akram 2007 [7]	USA	40	M	+/+	.	./.	-/.	./+	.	+
60	Akram 2007 [7]	USA	54	M	+/.	.	./.	-/.	+/.	.	+
61	Akram 2007 [7]	USA	67	M	+/.	.	./.	-/.	-/-	.	+
62	Akram 2007 [7]	USA	45	F	+/+	.	./.	-/.	+/.	.	+
63	Akram 2007 [7]	USA	59	M	+/.	.	./.	-/.	./+	.	+
64	Akram 2007 [7]	USA	75	M	+/+	.	./.	+/.	NT/.	.	+
65	Akram 2007 [7]	USA	59	F	+/+	.	./.	+/.	+/.	.	+
66	van Wanrooij 2021 [5]	NLD	23	F	+/-	T	+/-	-/-	+/-	.	+
67	van Wanrooij 2021 [5]	NLD	63	F	+/-	T	-/-	-/.	+/-	.	+
68	van Wanrooij 2021 [5]	NLD	36	F	+/+	T	+/+	-/-	-/?	.	+
69	van Wanrooij 2021 [5]	NLD	40	F	+/-	.	+/+	-/-	-/?	.	+
70	van Wanrooij 2021 [5]	NLD	67	M	+/-	T	-/-	-/-	+/-	.	+
71	van Wanrooij 2021 [5]	NLD	52	M	+/-	T	-/-	-/-	-/-	.	+
72	van Wanrooij 2021 [5]	NLD	57	M	+/.	T	+/+	-/-	-/-	.	+
73	van Wanrooij 2021 [5]	NLD	73	M	+/-	.	-/-	-/-	?/-	.	+
74	van Wanrooij 2021 [5]	NLD	59	M	+/-	T	+/+	-/-	+/-	.	+
75	van Wanrooij 2021 [5]	NLD	30	F	+/.	T	-/-	-/-	-/-	.	+
76	van Wanrooij 2021 [5]	NLD	52	F	+/.	T	-/-	-/.	-/-	.	+
77	van Wanrooij 2021 [5]	NLD	36	F	+/.	.	+/+	-/-	-/+	.	+
78	van Wanrooij 2021 [5]	NLD	39	F	+/-	T	-/-	-/-	+/-	.	+
79	Li 2024 [10]	CHN	39	F	./.	.	./.	./.	NT/NT	.	+
80	Li 2024 [10]	CHN	46	F	./.	.	./.	./.	NT/NT	.	+
81	Li 2024 [10]	CHN	44	F	./.	.	./.	./.	NT/NT	.	+
82	Li 2024 [10]	CHN	48	M	./.	.	./.	./.	NT/-	.	+
83	Li 2024 [10]	CHN	30	M	./.	.	./.	./.	NT/-	.	+
84	Li 2024 [10]	CHN	26	M	./.	.	./.	./.	NT/-	.	+
85	Li 2024 [10]	CHN	55	M	./.	.	./.	./.	NT/-	.	+
86	Li 2024 [10]	CHN	56	F	./.	.	./.	./.	NT/-	.	+
87	Li 2024 [10]	CHN	26	F	./.	.	./.	./.	-/NT	.	+
88	Li 2024 [10]	CHN	50	F	./.	.	./.	./.	-/NT	.	+
89	Li 2024 [10]	CHN	59	F	./.	.	./.	./.	NT/NT	.	+
90	Li 2024 [10]	CHN	22	F	./.	.	./.	./.	NT/NT	.	+
91	Li 2024 [10]	CHN	45	F	./.	.	./.	./.	NT/NT	.	+
92	Li 2024 [10]	CHN	33	F	./.	.	./.	./.	NT/NT	.	+
93	Li 2024 [10]	CHN	49	F	./.	.	./.	./.	NT/NT	.	+
94	Li 2024 [10]	CHN	60	M	./.	.	./.	./.	NT/NT	.	+
95	Masia 2014 [8]	USA/AUS	63	M	+/+	.	+/.	-/.	NT/NT	.	+
96	Masia 2014 [8]	USA/AUS	26	F	+/+	.	./.	-/.	NT/NT	.	+
97	Masia 2014 [8]	USA/AUS	72	M	+/+	.	./+	-/.	NT/NT	.	+
98	Masia 2014 [8]	USA/AUS	62	F	+/+	.	./.	-/.	NT/NT	.	+

(Contd...)

Supplementary Table 3A *(Continued)*

Case	Study [ref.]	Ctry	Age (years)	Sex	SB/ Col	VA	Gb/Pa	tTG/ EMA	AEA/ AGCA	MisDx	Criteria
99	Masia 2014 [8]	USA/AUS	74	F	+/-	.	./.	-/.	NT/NT	.	+
100	Masia 2014 [8]	USA/AUS	80	M	+/-	.	./.	-/.	NT/NT	.	+
101	Masia 2014 [8]	USA/AUS	65	F	+/+	.	./.	-/.	-/NT	.	+
102	Masia 2014 [8]	USA/AUS	49	F	+/+	.	./.	-/.	+/NT	.	+
103	Villanacci 2019 [52]	ITA	65	F	+/.	.	./.	./.	+/.	.	+
104	Villanacci 2019 [52]	ITA	28	F	+/.	.	./.	./.	-/.	.	+
105	Villanacci 2019 [52]	ITA	55	F	+/.	.	./.	./.	-/.	.	+
106	Villanacci 2019 [52]	ITA	28	M	+/.	.	./.	./.	./.	.	+
107	Villanacci 2019 [52]	ITA	57	F	+/.	.	./.	./.	-/.	.	+
108	Villanacci 2019 [52]	ITA	46	F	+/.	.	./.	./.	-/.	.	+
109	Villanacci 2019 [52]	ITA	48	M	+/.	.	./.	./.	-/.	.	+
110	Villanacci 2019 [52]	ITA	54	F	+/.	.	./.	./.	-/.	.	+
111	Villanacci 2019 [52]	ITA	23	M	+/.	.	./.	./.	-/.	.	+
112	Villanacci 2019 [52]	ITA	45	F	+/.	.	./.	./.	-/.	.	+
113	Villanacci 2019 [52]	ITA	30	M	+/.	.	./.	./.	-/.	.	+
114	Villanacci 2019 [52]	ITA	28	M	+/.	.	./.	./.	-/.	.	+
115	Villanacci 2019 [52]	ITA	73	M	+/.	.	./.	./.	./.	.	+
116	Villanacci 2019 [52]	ITA	18	M	+/.	.	./.	./.	NT/.	.	+
117	Villanacci 2019 [52]	ITA	45	F	+/.	.	./.	./.	./.	.	+
118	Villanacci 2019 [52]	ITA	18	M	+/.	.	./.	./.	NT/.	.	+
119	Villanacci 2019 [52]	ITA	63	F	+/.	.	./.	./.	NT/.	.	+

Each row represents a unique extracted adult case (n=119). Variables summarize key diagnostic elements reported in the source publication(s), including demographics, anatomic extent, villous atrophy grading (when provided), epithelial lineage abnormalities (goblet and Paneth cell loss), celiac serologies (tTG IgA, EMA), anti-enterocyte/anti-goblet cell antibody testing (when reported), and documentation of an initial alternative diagnosis. Blank fields indicate that an element was not reported or was not extractable from the publication

Legend: "+" indicates present/positive; "-" indicates absent/negative; NT, not tested; "?", unclear; NR, not reported. *SB/Col, small bowel/colon involvement; VA, villous atrophy grade (T, total/flat; S, subtotal/severe; P, partial/mild; U, ungraded; P–T, mixed partial-to-total); Gb/Pa, goblet/Paneth cell loss; tTG/EMA, tissue transglutaminase IgA/endomysial antibody; AEA/AGCA, anti-enterocyte/anti-goblet cell antibodies; MisDx, initial alternative diagnosis (CeD, celiac disease; IBD, inflammatory bowel disease; Inf, infection; Med, medication-related; ID, immunodeficiency; Oth, other); Criteria, explicit diagnostic criteria stated*

Supplementary Table 3B Case-level treatment exposures, clinical course, and outcomes across included adult autoimmune enteropathy (AIE) cases

Case	Study [ref.]	Tx	Resp	FU/Rel/Death	COD
1	Society of Hospital Medicine 2012 [36]	Ster,IFX,PN	.	././.	.
2	von Hahn 2005 [29]	Ster,AZA,TAC,IFX,PN	C	+/+/.	.
3	Xu 2014 [38]	Ster,AZA,PN	.	5.7/./-	.
4	Klinger 2015 [40]	Ster,Bud	I	././.	.
5	Lei NR [54]	Ster,Bud,IFX,VDZ,UST,PN	I	././.	.
6	Mitomi 1998 [21]	Ster,PN	P	+/+/+	Candidiasis/sepsis
7	Ranta 2010 [32]	Ster,IFX,PN	.	14/-/-	.
8	Rogahn 1999 [23]	Ster,TAC,CsA,IVIG,PN	0	+/./+	Sepsis
9	McCabe 2017 [45]	Ster,Bud,IFX,ADA,PN	.	12/+/.	.
10	Soma 2020 [55]	Ster,IFX,ADA,PN	C	6/./-	.
11	Lundholm 2019 [50]	Ster,Bud,PN	C	6/-/-	.

(Contd...)

Supplementary Table 3B *(Continued)*

Case	Study [ref.]	Tx	Resp	FU/Rel/Death	COD
12	Lorentsen 2023 [65]	Ster,Bud,AZA,PN	C	+/+/.	.
13	Lie 2017 [44]	Ster,PN	.	3.5/-/.	.
14	Iaquinto 2021 [58]	Ster,PN	C	14/./-	.
15	Mais 1999 [22]	.	C	24/-/+	Resp fail (MG)
16	Corazza 1997 [2]	Ster	I	18/./+	MI
17	Daum 2003 [26]	Ster,TAC,CsA,PN	I	24/+/.	.
18	Du 2021 [57]	Ster	C	3/./-	.
19	Zhou 2021 [60]	Ster,AZA,TAC	P	+/+/.	.
20	Scheid 2021 [59]	Ster,Bud,AZA,UST,PN	C	9/-/.	.
21	Fidias 2015 [39]	Ster,CsA,IVIG	P	24/+/.	.
22	Gerqari 2025 [70]	Ster	.	+/./.	.
23	Giblen 2024 [67]	Bud	.	+/./.	.
24	Hasan 2016 [43]	Ster,ADA	I	1/./.	.
25	Carroccio 2003 [25]	Ster,Bud	C	+/-/-	.
26	Carvalho 2023 [63]	Ster,AZA	C	+/+/.	.
27	Casis 2002 [24]	Ster	.	24/+/+	MODS
28	Chetty 2019 [49]	.	P	+/./.	.
29	Chlorakis 2025 [69]	Ster,AZA,IVIG,PN	.	+/-/-	.
30	Trivedi 2019 [51]	Ster,Bud,IFX,ADA,PN	C	+/+/.	.
31	Ciccocioppo 2018 [46]	Ster	C	+/+/+	Sepsis
32	Ciccocioppo 2012 [35]	Ster,Bud,PN	C	22/+/.	.
33	Colizzo 2022 [61]	Ster,Bud,TAC,CsA,VDZ	C	8/+/-	.
34	Elwing 2005 [28]	Ster,IFX,PN	C	10/-/-	.
35	Bishu 2011 [33]	Ster	C	26/./.	.
36	Xu 2023 [66]	Ster,AZA	C	24/+/.	.
37	Correia 2023 [64]	Ster,AZA	I	12/./.	.
38	Chong 2021 [56]	Ster,CsA,IVIG,PN	I	+/+/.	.
39	Depince-Berger 2016 [42]	Ster,IFX,PN	.	+/./.	.
40	Patel 2024 [68]	Ster,PN	P	4/./-	.
41	Khalidi 2006 [30]	Ster,PN	.	4/./.	.
42	Amer 2023 [62]	Ster,AZA	C	+/+/.	.
43	Chuang 2013 [37]	Ster,AZA,IFX	C	24/+/.	.
44	Isaac-Coss 2025 [71]	Ster,VDZ	C	+/-/.	.
45	Beck 2020 [53]	Ster,Bud,CsA,VDZ	0	+/./+	Aspergillus shock
46	Ashley 2004 [27]	Ster,TAC,PN	C	+/-/.	.
47	Pérez 2010 [31]	Ster,PN	C	8/./.	.
48	Salas Antón 2018 [47]	Ster,AZA,IFX,ADA	C	33/./.	.
49	Riquelme 2015 [41]	Ster,PN	C	9/./.	.
50	Rodriguez 2018 [48]	Ster,Bud,TAC,IFX,ADA,PN	I	+/./.	.
51	Akram 2007 [7]	Ster,Bud,AZA,IFX	C	24/./.	.
52	Akram 2007 [7]	Ster,AZA	C	19.2/./.	.
53	Akram 2007 [7]	Ster,Bud	C	12/./.	.

(Contd...)

Supplementary Table 3B *(Continued)*

Case	Study [ref.]	Tx	Resp	FU/Rel/Death	COD
54	Akram 2007 [7]	Ster,AZA,TAC,CsA,IFX	C	12/./.	.
55	Akram 2007 [7]	Bud,AZA	P	420/./.	.
56	Akram 2007 [7]	Ster	C	24/./.	.
57	Akram 2007 [7]	Ster,Bud	C	204/./.	.
58	Akram 2007 [7]	Ster,Bud,AZA	C	164.4/./.	.
59	Akram 2007 [7]	Ster	.	6/./.	.
60	Akram 2007 [7]	Ster	C	6/./.	.
61	Akram 2007 [7]	Ster,AZA,IVIG	P	45.6/./.	.
62	Akram 2007 [7]	Ster	P	57.6/./.	.
63	Akram 2007 [7]	Ster	C	42/./.	.
64	Akram 2007 [7]	Ster, Bud	.	24/./.	.
65	Akram 2007 [7]	Ster	.	14.4/./.	.
66	van Wanrooij 2021 [5]	Ster,CsA,PN	C	140/./.	.
67	van Wanrooij 2021 [5]	.	.	+/./.	.
68	van Wanrooij 2021 [5]	.	.	+/./.	.
69	van Wanrooij 2021 [5]	.	.	+/./.	.
70	van Wanrooij 2021 [5]	.	.	+/./.	.
71	van Wanrooij 2021 [5]	.	.	+/./.	.
72	van Wanrooij 2021 [5]	.	.	+/./.	.
73	van Wanrooij 2021 [5]	.	.	+/./.	.
74	van Wanrooij 2021 [5]	.	.	+/./.	.
75	van Wanrooij 2021 [5]	Ster	.	+/./.	.
76	van Wanrooij 2021 [5]	Ster	.	+/./.	.
77	van Wanrooij 2021 [5]	Ster	.	+/./.	.
78	van Wanrooij 2021 [5]	Ster	.	+/./.	.
79	Li 2024 [10]	Ster	.	+/./.	.
80	Li 2024 [10]	Ster	.	+/./.	.
81	Li 2024 [10]	Ster	.	+/./.	.
82	Li 2024 [10]	Ster	.	+/./.	.
83	Li 2024 [10]	Ster	.	+/./.	.
84	Li 2024 [10]	Ster	.	+/./.	.
85	Li 2024 [10]	Ster	.	+/./.	.
86	Li 2024 [10]	Ster	.	+/./.	.
87	Li 2024 [10]	Ster	.	+/./.	.
88	Li 2024 [10]	Ster	.	+/./.	.
89	Li 2024 [10]	Ster	.	+/./.	.
90	Li 2024 [10]	.	.	+/./.	.
91	Li 2024 [10]	.	.	+/./.	.
92	Li 2024 [10]	.	.	+/./.	.
93	Li 2024 [10]	.	.	+/./.	.
94	Li 2024 [10]	.	.	+/./.	.
95	Masia 2014 [8]	.	.	+/./.	.

(Contd...)

Supplementary Table 3B *(Continued)*

Case	Study [ref.]	Tx	Resp	FU/Rel/Death	COD
96	Masia 2014 [8]	.	.	+/./.	.
97	Masia 2014 [8]	.	.	+/./.	.
98	Masia 2014 [8]	.	.	+/./.	.
99	Masia 2014 [8]	.	.	+/./.	.
100	Masia 2014 [8]	.	.	+/./.	.
101	Masia 2014 [8]	.	.	+/./.	.
102	Masia 2014 [8]	.	.	+/./.	.
103	Villanacci 2019 [52]	.	.	+/./.	.
104	Villanacci 2019 [52]	.	.	+/./.	.
105	Villanacci 2019 [52]	.	.	+/./.	.
106	Villanacci 2019 [52]	.	.	+/./.	.
107	Villanacci 2019 [52]	.	.	+/./.	.
108	Villanacci 2019 [52]	.	.	+/./.	.
109	Villanacci 2019 [52]	.	.	+/./.	.
110	Villanacci 2019 [52]	.	.	+/./.	.
111	Villanacci 2019 [52]	.	.	+/./.	.
112	Villanacci 2019 [52]	.	.	+/./.	.
113	Villanacci 2019 [52]	.	.	+/./.	.
114	Villanacci 2019 [52]	.	.	+/./.	.
115	Villanacci 2019 [52]	.	.	+/./.	.
116	Villanacci 2019 [52]	.	.	+/./.	.
117	Villanacci 2019 [52]	.	.	+/./.	.
118	Villanacci 2019 [52]	.	.	+/./.	.
119	Villanacci 2019 [52]	.	.	+/./.	.

Each row represents 1 unique extracted adult case (n=119). Treatments are not mutually exclusive and are recorded only when exposure was explicitly stated in the source report; blanks indicate not reported. The table also summarizes reported clinical response, follow up (including follow-up duration when extractable), relapse, mortality, and cause of death when available

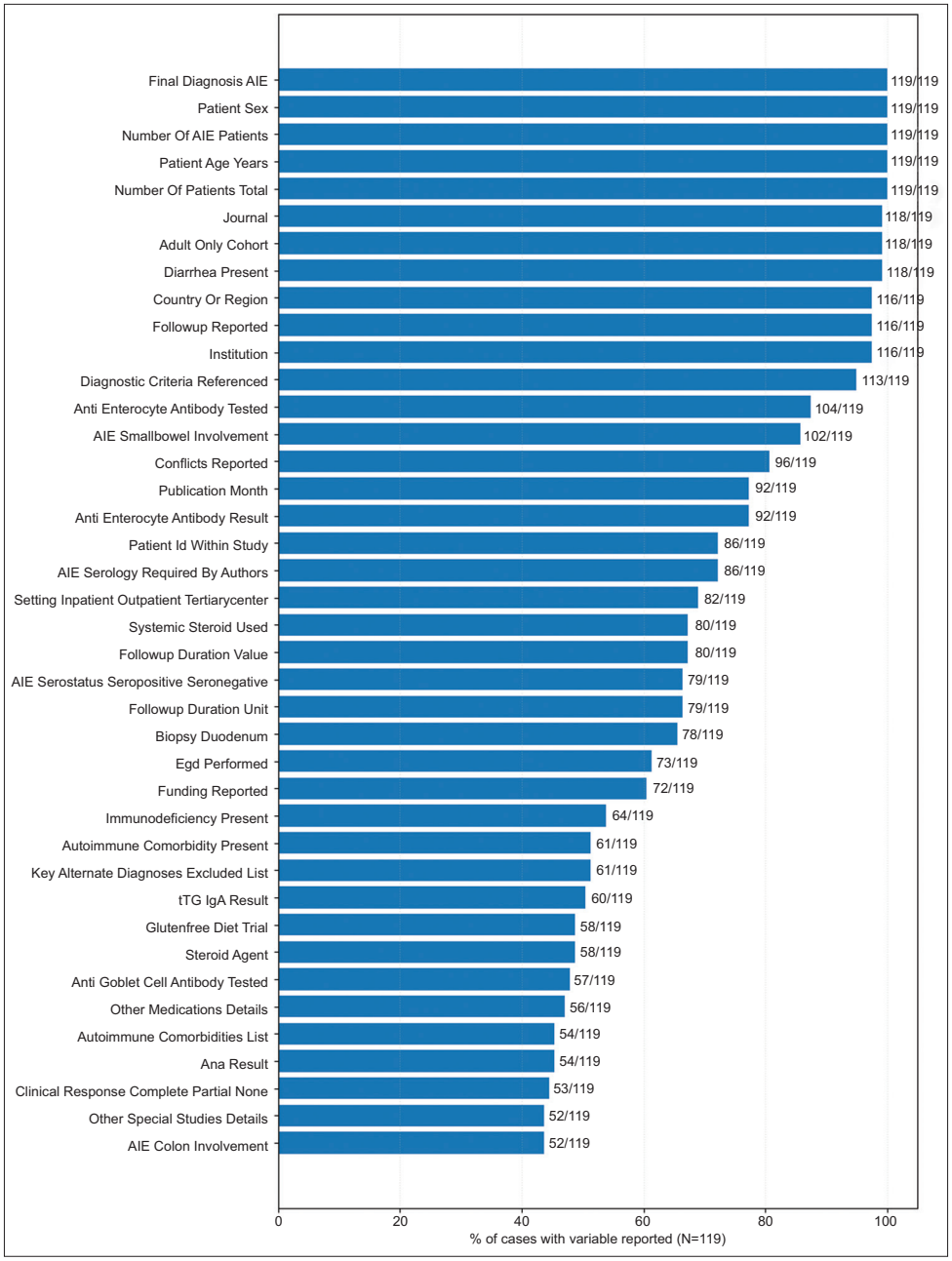
Legend: Tx=treatments used (when explicitly reported): Ster systemic steroids; Bud budesonide; AZA azathioprine; TAC tacrolimus; CsA cyclosporine; IFX infliximab; ADA adalimumab; VDZ vedolizumab; UST ustekinumab; IVIG intravenous immunoglobulin; PN parenteral nutrition. Resp=author-reported response: C complete; P partial; I improved/controlled (not clearly classifiable as complete/partial); 0 no response; not reported. FU/Rel/Death=follow-up duration in months (or + follow up reported but duration not extractable)/relapse (+ yes; - no; . not reported)/death (+ yes; - no; . not reported). COD=cause of death (abbreviated); . not reported

Supplementary Table 4 Comparison of major adult autoimmune enteropathy (AIE) cohorts/series with the remaining case-level literature

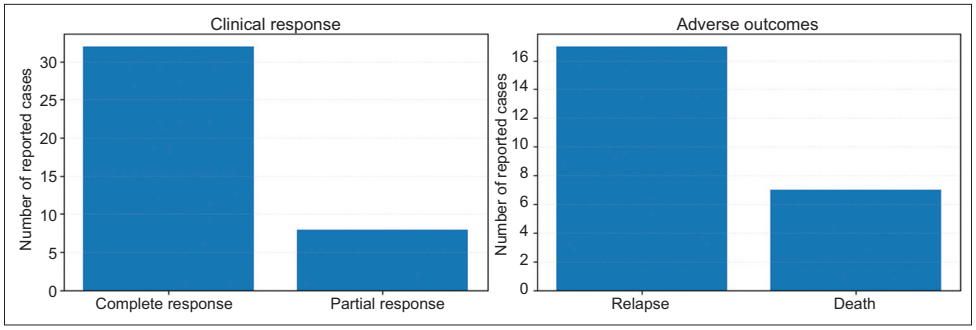
Study [ref.]	Region	n	Age, med (range)	Female	VA/Gb/Pa	tTG-/EMA-/AEA+	Tx	Rel/Death
Mu-Han Li (2024) [10]	China	16	46 (22-60)	11/16 (68.8%)	VA: NR Gb: NR Pa: NR	tTG-: NR EMA-: NR AEA+: 0/2 (0.0%)	Ster: 16/16 (100.0%) AZA: NR CNI: NR anti-TNF: NR	Rel: NR Death: NR
Vincenzo Villanacci (2019) [52]	Italy	17	48 (18-73)	9/17 (52.9%)	VA: NR Gb: NR Pa: NR	tTG-: NR EMA-: NR AEA+: 1/13 (7.7%)	Ster: NR AZA: NR CNI: NR anti-TNF: NR	Rel: NR Death: NR
Akram S (2007) [7]	United States	15	54 (37-76)	7/15 (46.7%)	VA: NR Gb: NR Pa: NR	tTG-: 10/15 (66.7%) EMA-: NR AEA+: 9/10 (90.0%)	Ster: 13/15 (86.7%) AZA: 6/15 (40.0%) CNI: 1/15 (6.7%) anti-TNF: 2/15 (13.4%)	Rel: NR Death: NR
Roy L.J. van Wanrooij (2021) [5]	Netherlands	13	52 (23-73)	8/13 (61.5%)	VA: 11/13 (84.6%) Gb: 7/13 (53.8%) Pa: 5/13 (38.5%)	tTG-: 13/13 (100.0%) EMA-: 11/11 (100.0%) AEA+: 6/7 (85.7%)	Ster: 3/3 (100.0%) AZA: NR CNI: 1/1 (100.0%) anti-TNF: 1/1 (100.0%)	Rel: NR Death: NR
Ricard Masia (2014) [8]	USA; Australia	8	64 (26-80)	6/8 (75.0%)	VA: 0/8 (0.0%) Gb: 1/1 (100.0%) Pa: 1/1 (100.0%)	tTG-: 8/8 (100.0%) EMA-: NR AEA+: 1/2 (50.0%)	Ster: NR AZA: NR CNI: NR anti-TNF: NR	Rel: NR Death: NR
Remaining literature	NR	50	50 (19-82)	29/50 (58.0%)	VA: 14/14 (100.0%) Gb: 7/8 (87.5%) Pa: 3/4 (75.0%)	tTG-: 8/9 (88.9%) EMA-: 10/10 (100.0%) AEA+: 18/27 (66.7%)	Ster: 46/46 (100.0%) AZA: 12/14 (85.7%) CNI: 8/9 (88.9%) anti-TNF: 13/15 (86.7%)	Rel: 17/27 (63.0%) Death: 7/18 (38.9%)

We summarize the largest included multi-patient adult AIE cohorts/series (defined here as publications contributing ≥8 extracted adult cases) alongside the remaining included publications (predominantly single-case reports/series). For each study/group, we report extracted adult case counts and selected diagnostic, serologic, treatment, and outcome features using explicit variable-specific denominators (n/N reported or n/N interpretable). "NR" indicates not reported/insufficient detail for extraction

Legend: Values are n/N (%), unless stated otherwise. VA=villous atrophy severity graded (partial/subtotal/total); Gb=goblet cell loss; Pa=Paneth cell loss; tTG=tissue transglutaminase IgA; EMA=endomysial antibody; AEA=anti-enterocyte antibody; Ster=systemic steroids; AZA=azathioprine; CNI=calcineurin inhibitor; anti-TNF=tumor necrosis factor inhibitor; Rel=relapse; NR=not reported



Supplementary Figure 1 Reporting completeness across key clinical variables. For each variable, bars show the percentage of included adult cases (N=119) with that item reported (i.e. not missing and not coded as "Not reported"). Values at the end of each bar indicate the number of cases with reporting (n/N). Variables shown represent the 30 most clinically relevant extracted fields



Supplementary Figure 2 Clinical outcomes reported in adult autoimmune enteropathy cases. Left, author-reported clinical response (complete vs. partial) among cases with response described. Right, relapse and death reported during follow up; outcomes are not mutually exclusive and denominators vary by outcome